REMARKS

Claims 1, 3-10, and 12-15 are pending. Claims 2, 11, and 16-19 are canceled.

Upon entry of claims presented in the response dated December 3, 2008, claims 1, 12, and 13 are amended.

Support for Amendments

Claim 1 is amended to include a preferred dose range for Et 743. Support can be found in the specification as originally filed, for example at page 7, 2nd full paragraph, page 10, Example 1, last paragraph, page 14, Example 2, middle paragraph, and page 15, Table 4. Claims 12 and 13 are amended for grammatical reasons, and to remove the word "about" with regard to various embodiments. No new matter is added.

Advisory Action of December 19, 2008

The Advisory Action of December 19, 2008 states that the arguments submitted December 3, 2008 "are not persuasive because the proposed amendment AFTER FINAL will not be entered" (Advisory Action, p. 2). Upon submission of the accompanying RCE, Applicants understand that the amendments will be entered as a matter of right. Therefore, Applicants understand that the arguments presented in the Advisory Action are moot as directed to the previous set of claims rather than the claims as currently amended.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-10, and 12-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/36135 (Takahashi) and WO 00/69441 (Bowman) in view of Dorr (Cancer

Chemotherapy Handbook, 1994, pages 395-416).[1] The Office Action argues that it would have been obvious to use the dosing schedules for doxorubicin as provided by Dorr in combination with the teachings of Takahashi and Bowman for the use of Ecteinascidin 743. The Office Action further asserts that one of ordinary skill in the art would have an expectation that the toxicity of doxorubicin as a single agent would not be affected by an agent with a different mechanism of action, and therefore one would look to the dosage of doxorubicin as a single agent for guidance in determining the dosage of doxorubicin in combination with another agent.

Applicants respectfully traverse the rejection on the basis that 1) the references, either alone or in combination, fail to teach the claimed dose range for Et 743 in combination with doxorubicin; 2) the literature does not support the Office Action's findings with respect to the toxicity of doxorubicin when used in combination with agents with different mechanisms of action; and 3) Applicants have surprisingly found evidence of unexpected results within a sub-range that rebut any case of obviousness that may have been made.

The References Fail to Teach the Claimed Dose of Between 0.6 and 0.75 mg/m^2 for Et 743

The Office Action cites Bowman with respect to meeting the claimed dose for Et 743 in combination with doxorubicin. However, Bowman actually teaches a "recommended dose level of 1500 microgram per m2 of body surface area for 24hr infusions or 1650 microgram per m2 body surface area for 3 hr infusions" (see Bowman, page 12, lines 22-24). Moreover, for the 24 hour infusion, Bowman teaches a preferred range of "between 1000 and 1500 microgram per m2 of body surface area," the latter being the RD (Recommended Dose) "as determined in clinical trials" (see Bowman, page 13, lines 14-18). For the 3 hr infusion, Bowman teaches a preferred

[1] Applicants note that the national phase entry of Takahashi is currently pending before the USPTO as US 10/416,086, and the national phase of Bowman is currently pending before the USPTO as US 09/787,461.

range "between 1000 and 1650 microgram per m2 of body surface area," the latter being the RD (Recommended Dose) "as determined in clinical trials" (see Bowman, page 13, line 19 through page 14, line 2). To be perfectly clear, both "between 1000 and 1500 micrograms per m2" and "between 1000 and 1650 microgram per m2 of body surface area" are outside the claimed range of 0.6 to 0.75 mg/m^2. In other words, at no point does Bowman teach the specifically claimed dose of "between 0.6 and 0.75 mg/m^2" for Et 743.

As shown above, Bowman fails to teach the claimed dose of between 0.6 and 0.75 mg/m^2 for Et 743, let alone the claimed dose of Et 743 in combination with about 50 mg/m^2 or about 60 mg/m^2 of doxorubicin. The deficiency of Bowman is not remedied by either Takahashi or Dorr. As a result, the Office Action can only arrive at the claimed elements through hindsight reconstruction of Applicants' claimed invention, which is clearly improper. Therefore, Applicants respectfully request withdrawal of the rejection.

In addition to the failure of the references to teach the claimed range of Et 743, Applicants find no support for the Office Action's argument that 60-75 mg/m^2 of doxorubicin from Dorr (page 399, table on lines 38-45) is equal to about 50 mg/m^2 as claimed (see Office Action, page 6, lines 17-20). In other words, this extension of the teachings of Dorr can only be arrived at through the Examiner's hindsight reconstruction of Applicants' claimed invention, which is clearly improper.

The Literature Does Not Support the Office Action's Findings Regarding Doxorubicin

In the response dated April 28, 2008, Applicants argued that one would not properly combine Dorr with either Takahashi or Bowman because Dorr teaches amounts of doxorubicin as a single agent rather than in combination with other agents, and that it was known in the art

that doxorubicin in combination with other anticancer agents may result in antagonism between the two agents. As evidence in support of this argument, Applicants cited Hahn et al. (see IDS of April 28, 2008), which reports less-than-additive (possibly antagonistic) cytotoxicity for the combination of paclitaxel (Taxol®) with doxorubicin against cell lines of human breast cancer, human lung adenocarcinoma and human ovarian cancer. Each drug when given alone is known to be active against these tumor types, but from the results, Hahn concludes that certain protocols of doxorubicin and paclitaxel "would have a reduced therapeutic index because the normal tissue toxicities might be additive for the combination drug regimen," (page 2711, left column, third full paragraph). In other words, Applicants have provided evidence that the combination of doxorubicin and a second antitumor agent results in increased side effects which limit the therapeutic index of the combination.

In response, the Office Action improperly ignores the evidence provided in Hahn, and argues that Dorr teaches that the "dose limit must take into account (page 399, right column, paragraph 4) due to having the same mechanism of action (page 396, left column, paragraph 3)" (see Office Action, page 7, lines 18-20). The Office Action concludes that "one of ordinary skill in the art at the time of the invention would have a reasonable expectation that an agent that has a mechanism of action that is certainly different from doxorubicin, such as ET-743, would not affect the dose limit of doxorubicin," (Office Action, page 8, lines 3-6). Moreover, the Office Action concludes that one of ordinary skill in the art "having an expectation that the dose limit would not be affected, would look to the dosage amount of the single agent doxorubicin as guidance for the dosage for doxorubicin in combination with an agent that has a different mechanism of action," (Office Action, page 8, lines 6-9). However, the Office Action provides no evidence from the literature to support this assertion. For the record, Applicants note that

paclitaxel, which was discussed in Applicants' previous comments on Hahn, has a different mechanism of action than doxorubicin.[2] Therefore, Applicants assert that based on the evidence already of record which was improperly not considered, the Office Action's conclusions with respect to doxorubicin dosage are contrary to the scientific literature.

In addition to the evidence already of record, Applicants note the following. Doxorubicin is an anthracycline antibiotic which intercalates between base pairs in the DNA helix, thereby preventing DNA replication and ultimately inhibiting protein synthesis (a DNA-intercalating compound). ET-743 is the first of a new class of anti-tumor agents with a complex transcription-targeted mechanism of action. A detailed description of the mechanism of action of Et 743 can be found, for example, in Lau et al. (Clinical Research, vol. 11, 672-77, 2005, provided previously). Therefore, the literature supports the proposition that doxorubicin and ET-743 have different mechanisms of action. However, contrary to the Examiner's opinion, the finding of an effective dosage for ET-743 and doxorubicin when they are administered together is not simply based on the dosage of doxorubicin as a single agent because it is known in the art that doxorubicin in combination with other anticancer agents, having the same or a different mechanism of action, may not be beneficial or may require changes in dose.

In Dorr, it is disclosed that drug interactions have been described when doxorubicin is administered with interpheron alpha and "substantial dose reductions are required" (Dorr, p. 400, paragraph linking first and second columns). Furthermore, a Phase I study of α2-Interferon plus doxorubicin in patients with solid tumors is described in the literature, wherein haematological toxicity was the dose limiting toxicity (see Sarosy et al., Cancer Research, vol. 46, 5368-5371, 1986). Sarosy concludes that "the concomitant administration of recombinant α2-Interferon

[2] Paclitaxel interferes with the normal function of microtubule breakdown- see, for example, the NCI drug dictionary (http://www.cancer.gov/drugdictionary/), while doxorubicin is a DNA-intercalating compound.

severely limits the amount of doxorubicin that can be administered" (see abstract). Moreover, Sarosy teaches that although prior *in vitro* and *in vivo* data showed that doxorubicin and interferon have synergistic antitumor activity, the concomitant administration of both drugs "severely limits the amount of doxorubicin that can be given." (Sarosy, last paragraph of the first column, page 5370). As evidence, Sarosy compares the maximum tolerated doses of doxorubicin in combination with interferon and as a single agent. Given concomitantly with interpheron alpha every 3 weeks, the maximum tolerated dose (MTD) for doxorubicin is 40 mg/m2, which is a dosage distinctly lower than the MTD for doxorubicin as a single agent (60-90 mg/m2) for the same administration schedule. Therefore, the combination therapy using doxorubicin and interferon alpha presented side effects (*i.e.*, myelosupression) which made it necessary to reduce doxorubicin dosage. Notably, the two agents have different mechanisms of action, where interpheron alpha binds to specific cell-surface receptors resulting in the transcription and translation of genes containing an interferon-specific response element, while doxorubicin is a DNA-intercalating antitumor agent. Therefore, the combination of doxorubicin with an anticancer drug having a different mechanism of action (e.g., interpheron alpha) may be unfavorable and require the reduction of the dosage of doxorubicin.

Similarly, undesired side effects have been observed when combining doxorubicin with vincristine, which is a natural alkaloid with antimitotic and antineoplastic activities which binds irreversibly to microtubules and spindle proteins in S phase of the cell cycle (an antimitotic agent). Neurotoxic side effects have been reported for administration of doxorubicin and vincristine as a combined anticancer therapy (see Boranic et al., Biomedicine, 31(5), 124-5, 1979). Boranic discloses a clinical case wherein central nervous system toxicity appeared after treating a child with acute leukemia with doxorubicin (Adriamycin) and vincristine:

> We have observed symptoms of an acute extrapyramidal lesion in a child with leukaemia treated with vincristine and adriamycin, and assume we have encountered another uncommon case of toxicity to the central nervous system. Vincristine usually causes peripheral neuropathies, while adriamycin inflicts damage to the heart

(Boranic, page 124, lines 4-10).

Moreover, combining doxorubicin and paclitaxel may result in undesired toxicity, as noted above by Hahn. It has also been reported that paclitaxel potentiates the cardiotoxicity of doxorubicin by decreasing its clearance. See, for example, Perotti *et al.* (Expert Opin Drug Saf, 2(1), 59-71, 2003). Perotti reviews the cardiotoxic effects of anthracycline-taxane combinations. The combination of paclitaxel with anthracycline is analysed in section 4, page 62. In particular, section 4.1 discloses the toxicity interactions of the doxorubicin-paclitaxel combination observed in clinical studies, when given at different doses by different schedules and at different sequences. In section 4.4, page 67, the enhancement of anthracycline toxicity by taxanes is analyzed from a mechanistic view.

In fact, the literature teaches that one of ordinary skill in the art would not assume that the dosage of a single agent would be tolerated in combination chemotherapy. For example, see Chabner et al., Cancer Chemotherapy and Biotherapy: Principles and Practice, Third Edition, 2001, pages 1-16, submitted herewith. Chabner teaches that specific drug interactions "must be considered in developing combination regimens" (p. 12, first full paragraph). Chabner further teaches that these interactions "may take the form of pharmacokinetic, cytokinetic or biochemical effects of one drug that influence the effectiveness of a second component of a combination" where "[p]atterns of overlapping toxicity are a primary concern" (p. 12, first full paragraph). Chabner provides several examples of cancer drug interactions at the excretion and metabolism level. Moreover, in the section "Dose Adjustment Based On Toxicity," Chabner emphasizes that drug combination regimens require dose-adjustment according to toxicity,

especially if over-lapping toxicity patterns are present. Finally, Chabner discusses the cardiotoxic effects of the combination of doxorubicin with trastuzumab (see page 13, right column, last paragraph). Chabner teaches that various combinations have "considerable promise based on the nonoverlapping toxicities and the differing modes of action of these classes of agents," but ultimately reports that in clinical trials, the combination of trastuzumab with doxorubicin/cyclophosphamide "demonstrated an unacceptable rate of cardiotoxicity." Chabner concludes that the toxic interaction between doxorubicin and trastuzumab "illustrates the point that, until drug and biologic combinations are tested clinically, one cannot assume that patterns of toxicity of individual agents will be unaffected by their combined use" (Chabner, page 14, left column, lines 5-8).

Thus, in view of the cited prior art, which teaches an adverse interaction between doxorubicin and other anticancer drugs, a person skilled in the art at the time of the invention would not have looked to the teachings of the single agent doxorubicin dose in Dorr for dosage information when embarking on a combination therapy using ET-743 and doxorubicin for the effective treatment of cancer in human patients. In other words, the technical literature does not support the Office Action's reliance on Dorr for determining the dosage of doxorubicin for the claimed combination. On this basis, Applicants respectfully request withdrawal of the rejection.

Evidence of Unexpected Results That Rebut Any Case of Obviousness

Applicants traverse the finding of obviousness. For example, the Office Action provides no basis in the literature for asserting that one would look to the dosage of doxorubicin as a single active agent when contemplating a combination therapy using ET-743 and doxorubicin. However, even if, for the sake of argument, a *prima facie* case of obviousness had been made in

the Office Action, Applicants have surprisingly found evidence of unexpected results within a sub-range that rebuts any case of obviousness that may have been made. As noted by the Federal Circuit, "[t]he law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). In the present case, Applicants have found that the combination of Et 743 in a dose range of 0.6 to 0.75 mg/m^2 for ET-743, and doxorubicin in a dose of about 50 mg/m^2 or about 60 mg/m^2 results in antitumor activity without dose-limiting toxicity. See Table 3 on page 13 of the specification as filed, which shows that five patients had confirmed partial response, and 5 patients had long-lasting stable disease after treatment as claimed. Table 4 in the specification as filed provides additional dose-limiting toxicity data. As discussed above, Applicants have provided ample evidence of combinations with doxorubicin resulting in undesired toxicity. Therefore, Applicants have found a sub-range that rebuts any case of obviousness that may have been made, and respectfully request withdrawal of the rejection.

Provisional Obviousness-Type Double-Patenting

Claims 1 and 3-9 are provisionally rejected for obviousness-type double patenting over claims 1-11 and 19-20 of US 11/577,790.

Because the rejections are provisional, Applicants respectfully request that the rejections be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejections and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105020. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105020.

Respectfully submitted,
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